REMARKS

Claims 1-25 were pending in the present application. Of these, claims 7-19 and 21-23 have been withdrawn from consideration, leaving claims 1-6, 20, and 24-25 pending and under examination. No amendments are made herein and thus, no new matter has been introduced.

November 26, 2008 Final Office Action

Previous rejections

Applicants note that no previous rejections have been maintained in the present Final Office Action.

In response, Applicants appreciate and acknowledge the Office Action's withdrawal of said previous rejections.

Rejections Under 35 U.S.C. §103

Claims 1-6, 20, 24, and 25 were rejected under 35 U.S.C. §103, as allegedly being obvious over Edwardson, et al. (U.S. 5,750,657), in view of Pfirrmann (U.S. 5,819,748) or Beisel (US 2006/0141007 A1).

According to the Office Action, Edwardson teaches a composition comprising fibrin sealant and antibiotic agents. The Office Action directed attention to the abstract, to column 22, lines 25-61 and to claims 1, 17, 30, and 31. The Office Action acknowledged that Edwardson does not expressly teach specific antibiotic agents that include methylol transefer agensts such as taurolidine or taurultam.

The Office Action stated that Pfirrmann teaches antibacterial substances including taurolidine or taurultam, and directed attention to column 1, lines 25-35.

The Office Action stated that Beisel teaches an antibiotic agent, including cefotaxime or taurolidine (directing attention to paragraph 0029).

The Office Action then concluded that, on the basis of the above, "it would have been obvious to one of ordinary skill in the art to modify the fibrin sealant composition of Edwardson to include taurolidine and/or taurultam to obtain the claimed invention." The Office Action stated that "[t]his is because Pfirrmann teaches the advantageous results in the use of taurolidine and taurultam over antibiotic [sic] such as gentamycin (ID), because Pfirrmann teaches taurolidine and taurultam provide an extremely effective implant material (ID), because Beisel teaches that taurolidine is a well known antibiotic agent, and because Edwardson teaches the desirability for using antibiotic agents in the fibrin sealant composition." (Office Action page 2).

The Office Action also further acknowledged that Edwardson does not expressly teach the concentration of the antibiotic agent in the composition. The Office Action asserted, however, that differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. In that regard, the Office Action stated that "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." On this basis, the Office Action concluded it would have been obvious to, by routine experimentation, determine a suitable amount of antibiotic agent for the composition, depending on the desired use. The Office Action further stated that "Edwardson teaches a fibrin sealant composition comprising antibiotic suitable for a wide variety of use," directing attention

again to claim 31.

In response, Applicants respectfully traverse the obviousness rejection set forth in the Office Action. First, Applicants reiterate that the presently claimed invention is directed to, *inter alia*, an antineoplastic composition comprising an antineoplastic-effective amount of a methylol transfer agent (MTA) in combination with a biodegradable adhesive capable of adhering to tissue of a living subject. Nothing in the cited art, alone or in combination, suggests any such composition. Indeed, the Office Action does not even attempt to suggest it does. The Office Action is entirely devoted to discussion of antibacterially effective compositions, which is not Applicants' present invention.

Moreover, Applicants note that the portions of the Edwardson reference to which the Office Action directs attention do not teach what the Office Action asserts. Edwardson is directed to a fibrin sealant and methods of making such a sealant. It does mention that adjuvants, such as antibiotics, can be added to the sealant, but as the Office Action readily acknowledges, makes no specific mention of MTAs or, certainly, of any concentrations of any active substances, including even antibiotics. More importantly, however, as noted, Applicants' invention is directed to *anti-neoplastic* compositions comprising *anti-neoplastic-effective amounts* of an MTA. Neither Edwardson, nor any of the other cited art, suggests any such compositions. This is not a case where the "general conditions of a claim are disclosed in the prior art," and that all is needed is merely "routine experimentation" to "discover the optimum or workable ranges," as the Office Action has asserted. Edwardson refers in very general terms to "antibiotics" but reveals nothing even about what might be effective *antibiotic* amounts of such drugs. Given such lack of disclosure even with respect to *antibiotic* use, it cannot reasonably be

concluded that one could determine (or would even think of trying to determine) an *anti-neoplastic effective amount* of a specific type of *anti-neoplastic* agent, e.g., an MTA. Mere "routine optimization" would not lead one of only ordinary skill to Applicants' anti-neoplastic composition comprising an antineoplastic effective amount of an MTA. At best, one looking at Edwardson would have been seeking *antibacterially* effective amounts of an infinite number of antibiotics, not *antineoplastic*-effective amounts of an MTA.

Furthermore, neither Pfirrmann nor Beisel provides the teachings missing from Edwardson that would be required to support an obviousness rejection. Pfirrmann refers to a collagen based sponge material for use as an implant in bone surgery, to prevent re-infection of bone cavities following removal of bone in the treatment of osteomyelitis and osteitis. In that regard, the implant can comprise *antibacterially* effective amounts of antibiotics, such as taurultam or taurolidine, but does not even contemplate the usefulness of such agents as *anti-neoplastics* or in compositions such as those claimed herein. No combination of teachings from Edwardson and Pfirrmann would lead one of ordinary skill in the art to consider the anti-neoplastic compositions of the claimed invention.

Beisel is even further removed from Applicants' claimed invention. Beisel refers to weight reduction compositions for making one feel full by introducing a swellable compound packed with nutrients into the stomach. Beisel has nothing whatsoever to do with antineoplastic compositions such as those claimed herein. Beisel does make passing reference to tauraltam, again as an antibiotic agent, but does so in the midst of a list of hundreds of "active agents" that spans five printed columns of the published application. Not only would nobody of ordinary skill in the art ever think to combine the teachings of Beisel with that of Edwardson, even if one

did combine such teachings, one could not have arrived at Applicants' claimed *anti-neoplastic* compositions comprising *antineoplastic effective amounts* of MTA.

For at least the reasons set forth above, no combination of teachings of the cited references can render obvious Applicants' present claims.

Moreover, Applicants direct attention to the present specification, at paragraph [0016], wherein it is noted that all anti-tumor agents are not identical in their modes of action or biological effects. In particular, it is noted that methylol transfer is to be contrasted with methyl transfer, a characteristic of many highly toxic anti-tumor drugs. Exemplified methylol transfer agents of the present application are described in the specification as having low toxicity and not having cytotoxicity against normal cells. The present invention allows the delivery of the drug in therapeutically effective concentrations with minimal toxic effects on healthy brain tissue. (See e.g. paragraph [0036]). The art of record simply does not allow one to reliably achieve this result. There is no guidance in any combination of teachings in the cited references that would lead one to conclude that a MTA would or even could be successfully employed in an amount that would be "anti-neoplastically effective" in the type of composition that is the subject of the Applicant's claimed invention. Thus, even if one were to combine teachings as the Office Action has done, there is no reasonable expectation that one could achieve an antineoplastic-effective amount of a methylol transfer agent (MTA) in combination with a biodegradable adhesive capable of adhering to tissue of a living subject, with mere routine experimentation or optimization of ranges.

Moreover, Applicants direct further attention to the important fact that the claims reflect the Applicants' unexpected findings that compositions containing the disclosed amounts of MTA

release antineoplastically effective amounts of the agent over the entirety of the expected 14 day life span of a fibrin sealant matrix. This is discussed, for example, at paragraph [0054] and surrounding disclosure, (with specific effective ranges also recited at paragraph [0028]), and confirmed by the *in vitro* results described elsewhere in the Example. It is an extremely beneficial result in terms of the therapeutic efficacy of the claimed compositions, and is one which cannot in any way be predicted from any of the prior art of record. Thus, for at least these additional reasons, the references cited in the Office Action, which focus entirely on the antibiotic effectiveness of certain compositons, provide no guidance whatsoever to one of ordinary skill in the art on how to obtain Applicants' claimed antineoplastic compositions, comprising antineoplastic effective amounts of an MTA. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103.

In view of the above remarks, Applicants believe the rejection set forth in the November 26, 2008 Final Office Action has been overcome and the application is in condition for allowance. The Office is invited to telephone the undersigned if it is deemed to expedite prosecution.

Respectfully submitted,

By _____

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